TABLE 1. Eligibility Requirements

Inclusion criteria

1. PTCA of a single, native coronary artery
2. Lesion types: de novo or restenotic
3. Treatment: balloon alone or stent implantation, at the operator's discretion
4. Lesion and vessel requirements: lesion length ≤15 mm; total treatment length (balloon or stent) ≤22 mm; reference vessel diameter ≥2.4 mm and ≤3.7 mm
5. Successful outcome of PTCA

Exclusion criteria

1. Patients receiving PTCA treatment to other coronary vessels within 60 days of the study procedure
2. Bifurcation lesions
3. Aorto-ostial lesions
4. Unprotected left main lesion ≥50% diameter stenosis
5. Dissection after PTCA that was not repaired by stent placement
6. Acute MI (creatine kinase ≥3×normal value) within 5 days
7. Cardiogenic shock
8. Prior therapeutic irradiation to the heart or target vessel area
9. Renal insufficiency
10. Unstable ventricular arrhythmias
11. Cancer or other serious medical illness, which could limit survival to <1 year
12. Previously diagnosed autoimmune disease

Radiation Delivery System

The intravascular radiation therapy system, dosimetry, and procedure have been described previously in detail.[6] Briefly, the system consists of 3 components. The source wire is a 0.018-inch flexible Nitinol wire, with the active ^{32}P source encapsulated in the distal 27 mm of the wire. The centering balloon catheter is a double-lumen catheter with a short monorail distal tip for a rapid exchange method of delivery and a spiral balloon, with nominal diameters of 2.5, 3.0, and 3.5 mm, which centers the source within the lumen while allowing side branch and distal perfusion (Figure 1).[7] The source delivery unit provides safe storage of the active wire and automated delivery and retrieval.

Procedure

After completing the angioplasty procedure, the centering catheter was advanced to the lesion site, and the markers were optimally positioned to straddle the balloon/stent-treated lesion segment. The centering balloon was inflated with normal saline, and a contrast injection was made through the guiding catheter to assess flow to the side branches and to the distal artery (Figure 2). An inactive wire was advanced into the centering catheter, its position was optimized, and it was withdrawn. Then the study wire (either active or placebo) was advanced to the same location as the inactive wire and verified angiographically.

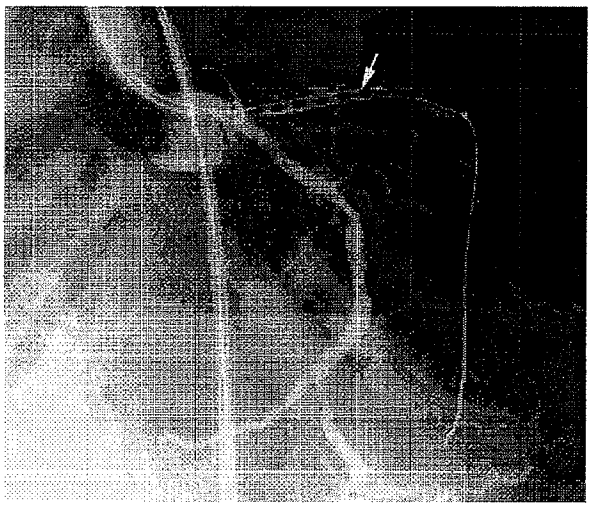

Figure 2. A centering balloon positioned in a left anterior descending coronary artery. With the balloon inflated (shown) the source is centered in the artery lumen (arrow). The inflated balloon allows passive side branch and distal coronary artery perfusion to accommodate prolonged treatment times.

Dosimetry

The radiation prescription was based on the average of the lumen diameters at the proximal and distal reference segments, as measured by intravascular ultrasound or online quantitative coronary angiography or as determined by the known percutaneous transluminal coronary angioplasty (PTCA) balloon or stent sizes. This value was entered into the source delivery unit, which then used source activity to calculate the dwell time needed to deliver the specified dose.

Randomization, Follow-Up, and Medication

Each patient was randomized to 1 of 4 radiation treatment groups: 0, 16, 20, or 24 Gy to 1 mm beyond the lumen surface. Only the radiation oncologist, medical physicist, and the radiation safety officer were not blinded to treatment assignment. Clinical follow-up

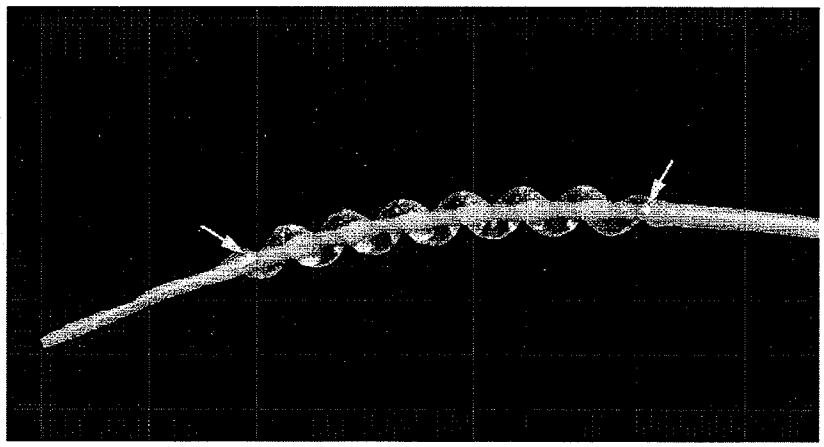

Figure 1. The rapid-exchange centering balloon catheter incorporates a spiral balloon to center the source. Radiopaque markers identify the radiation treatment zone (arrows). A closed lumen within the shaft serves as the conduit for the source wire, which is delivered by the source-delivery unit.

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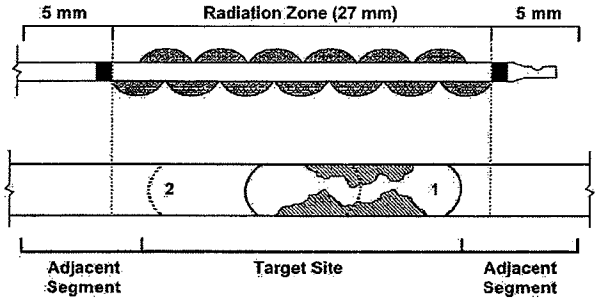

Figure 3. Schematic diagram of defined segments on quantitative coronary angiography. An example of a balloon is shown, which was inflated in 2 different positions (numbers 1 and 2) in the course of the procedure. The "target site" spans the length of these documented inflations.

was obtained at 1, 3, and 6 months. Angiographic follow-up was mandated after 6 months. All patients received 325 mg of aspirin for the duration of the study. Ticlopidine (250 mg BID) was prescribed for 4 weeks after the index procedure for patients who received a procedural stent.

Quantitative Coronary Angiography

After nitroglycerin administration, angiograms were obtained in ≥2 views at baseline (pre-PTCA), after the procedure, and at 6 months. Procedural and 6-month films were forwarded to the Core Angiography Laboratory at Baylor College of Medicine and were read in a blinded fashion using the CAAS II system (Pie Medical). Markers on the centering catheter identified the location of the radiation zone. The 6-month angiogram was analyzed with a side-by-side projection of the radiation treatment catheter to assure accurate identification of the radiation zone. Target site was defined as the segment of balloon and stent injury required to treat the target lesion. Adjacent segments were defined as the segments of artery outside the target site and extended to 5 mm beyond the radiation zone (Figure 3). Reference and minimal lumen diameters (MLD) and percent diameter stenosis of the target site and adjacent segment were determined. Acute gain, late lumen loss, and late loss index (expressed as a percent of acute gain) were calculated for the target site. Binary restenosis was defined as ≥50% diameter stenosis on the follow-up angiogram and was measured for target site alone and for target site plus adjacent segments.

End Points

All clinical events were reviewed and adjudicated by an independent Clinical Events Committee. The primary clinical end point was the combined short-term (in-hospital) and late (12 months) rate of major adverse clinical events (MACE). MACE were defined as the composite of death, myocardial infarction (MI; Q-wave and non–Q-wave), and target lesion revascularization (TLR; PTCA or coronary artery bypass grafting) for restenosis involving the target site. Secondary clinical end points included each of the individual MACE events, as well as target vessel revascularization (TVR) for restenosis involving the target site and adjacent segments. Angiographic end points were MLD, late lumen loss, late loss index, and binary restenosis at 6 months.

Statistical Methods

Analysis Population

The primary safety end point of the combined early and late rate of MACE was analyzed on a per protocol (successful procedure) basis. Three patients who were enrolled did not receive the randomized treatment because of equipment difficulties; they were excluded from analyses because none of them received any portion of the assigned radiation treatment.

The 3 radiation dose populations (16, 20, and 24 Gy) were pooled. Also, the 3 lesion types (de novo, PTCA restenosis, and in-stent restenosis) were pooled. Statistical differences were considered significant at $\alpha<0.05$.

TABLE 2. Baseline Clinical and Angiographic Charactistics

Characteristics	^{32}P Group (n=80)	Control Group (n=25)
Age, y	63±11	63±8
Male sex	51 (64)	19 (76)
Smokers	19 (24)	10 (40)
Diabetes mellitus	16 (20)	6 (24)
Hypertension requiring treatment	50 (63)	11 (44)
Hyperlipidemia requiring treatment	38 (48)	14 (56)
De novo lesion	54 (68)	19 (76)
Restenotic lesion	26 (33)	6 (24)
In-stent restenosis	19 (24)	6 (24)
Prior MI	28 (35)	14 (56)
CCS III or IV*	49 (69)	17 (71)
No. of diseased coronary arteries		
Single-vessel disease	52 (65)	18 (72)
Multivessel disease	28 (35)	7 (28)
Ejection fraction, %	60±11	58±16
Target vessel		
LAD	37 (46)	10 (40)
CFX	13 (16)	6 (24)
RCA	30 (38)	9 (36)
ACC/AHA lesion class	(n=76)	(n=25)
A	18 (24)	4 (16)
B_1	29 (38)	13 (52)
B_2	24 (31)	6 (24)
C	5 (7)	2 (8)

Values are mean±SD or n (%). CCS indicates Canadian Cardiovascular Society; LAD, left anterior descending; CFX, circumflex; RCA, right coronary artery; ACC, American College of Cardiology; and AHA, American Heart Association.

*n=71 in ^{32}P group and n=24 in control group.

Determination of Safety

The randomization was unbalanced (3:1) to detect any safety issues that would occur with radiation at a high frequency. Binary incidence rates, angiographic restenosis, target-related revascularization or failure, or combined nonspecific late ischemic end points were tested with χ^2 or exact contingency table analyses. Continuous variables were compared by Student's t test.

Results

A total of 105 patients were enrolled in the study and had a successful procedure; 25 were assigned to the control group and received a nonradioactive treatment wire (sham procedure), and 26, 27, and 27 patients were assigned to receive 16, 20, and 24 Gy, respectively.

The baseline clinical and angiographic characteristics of the treated and control patients are shown in Table 2. Overall, 73 patients (70%) had de novo lesions and 32 (30%) had restenotic lesions, which included those with in-stent restenosis (24%). The angioplasty procedure included placement of a new stent(s) in 64 patients (61%).

During centering balloon inflation, blood flow to the distal vessel and side branches was observed in 87% and 91% of

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TABLE 3. MACE at 12 Months

	Radiotherapy (n=80)	Control (n=25)	P
MACE (death, MI, TLR)	13 (16)	6 (24)	NS
MACE (death, MI, TVR)	21 (26)	8 (32)	NS
Death	1 (1)	0 (0)	NS
MI	8 (10)	1 (4)	NS
Q-wave	2 (3)	0 (0)	
Non–Q-wave	6 (7)	1 (4)	
TLR	5 (6)	6 (24)	<0.05
PTCA	4 (5)	5 (20)	
CABG	1 (1)	1 (4)	
TVR	17 (21)	8 (32)	NS
PTCA	14 (17)	6 (24)	
CABG	2 (4)	2 (8)	

Values are n (%). CABG indicates coronary artery bypass grafting.

patients, respectively. Fractionation of the treatment was required in only 9 patients (9%) to relieve ischemia during inflation of the centering balloon.

Source wire activity ranged from 39 to 146 mCi (mean, 70±22 mCi). Dwell time ranged from 1.0 to 9.6 minutes (mean, 4.6±2.0 minutes). The time added to the angioplasty procedure to perform radiotherapy was 12±6 minutes (range, 4 to 31 minutes). The radiation survey reading taken 1 m from the approximate location of the source during active source dwell time was 0.46±0.35 mrem/h (range, 0.04 to 1.52 mrem/h).

The primary clinical end point was combined early (in hospital) and late MACE. In-hospital events occurred in 1 radiotherapy patient (1.3%; non–Q-wave MI) and 1 control patient (4.0%; non–Q-wave MI) (P=NS). No in-hospital death or postprocedure revascularization occurred.

Long-term (12-month) MACE (death, MI, and TLR) occurred in 13 radiotherapy patients (16%) and 6 control patients (24%; P=NS). If TVR is included, MACE occurred in 21 radiotherapy patients (26%) and 8 control patients (32%; P=NS).

The occurrences of individual MACE are shown in Table 3. One patient in the radiotherapy group (16 Gy) died suddenly 2.5 months after receiving a stent for the treatment of a restenotic lesion in the right coronary artery. Ticlopidine was prematurely discontinued 3 weeks after the procedure because of an allergic reaction. At autopsy, thrombotic occlusion within and proximal to the stent was noted in the absence of significant neointimal growth. Two in-hospital procedure-related non–Q-wave MIs occurred, one in each treatment group. Seven additional MIs occurred in the radiotherapy group. These occurred at 5 (non–Q-wave), 23 (Q-wave), 83 (non–Q-wave), 103 (non–Q-wave), 111 (non–Q-wave), 160 (Q-wave) and 188 (non–Q-wave) days after the index procedure. All 7 posthospitalization MIs were considered acute occlusive events; 6 were treated with thrombolytic therapy and 1 by direct PTCA. Angiography, which was performed in 6 of the 7 patients, showed definite thrombus in 3. No definite thrombus was seen in 3 others whose angiograms were performed several hours (2 patients) or 3 days (1 patient) after receiving thrombolytics. Each of these 3 patients had restenosis involving the adjacent segment. Six of the 7 patients with posthospitalization MIs received new stents at the index procedure. No late MIs occurred in the control group.

TLR for restenosis was significantly lower in the radiotherapy group (6%) than in the control group (24%; P<0.05). A trend existed toward a lower incidence of TVR in the radiotherapy patients (21% versus 32%), which was not significant by statistical criteria.

The results of the quantitative coronary angiography analysis are summarized in Table 4 and Figure 4. At the 6-month follow-up angiographic examination, late lumen loss was 0.22±0.6 mm for the radiotherapy patients compared with 1.1±0.7 mm for controls (P<0.0001), and the late loss index was 11±36% compared with 55±30% (P<0.00001). No coronary artery aneurysms or nonhealed dissections were seen on follow-up angiography.

Angiographic restenosis (≥50% diameter stenosis) of the target site was 8% for radiotherapy patients compared with

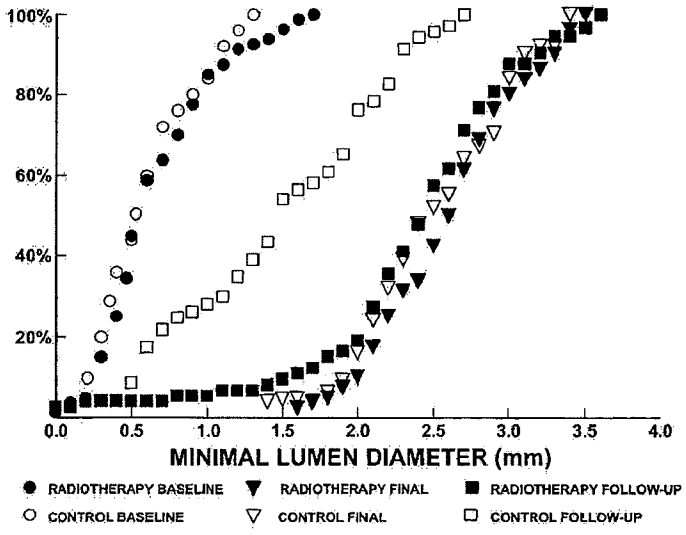

Figure 4. The cumulative distribution curves of the MLD before and after the index revascularization procedure and at 6-month follow-up angiography. The percentage on the vertical axis indicates the fraction of patients who presented with an MLD equal to or smaller than a given value on the horizontal axis. The curves are similar for the radiotherapy and control groups before and after the procedure. However, at 6 months, the control patients had regressed toward preprocedure MLD values, whereas the radiotherapy patients remained close to the postprocedure MLD curve.

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TABLE 4. Quantitative Coronary Angiographic Analysis

	^{32}P Group (n=80)	Control (n=25)	P
Baseline			
Reference vessel diameter, mm	2.99±0.48	2.97±0.55	NS
MLD, mm	0.74±0.37	0.68±0.31	NS
Percent diameter stenosis, %	75±11	77±8	NS
Postprocedure			
Reference vessel diameter, mm	3.23±0.42	3.20±0.53	NS
MLD, mm	2.68±0.49	2.60±0.51	NS
Percent diameter stenosis, %	17±9	19±9	NS
At 6-month follow-up	(n=73)	(n=23)	
Reference vessel diameter, mm	3.08±0.45	2.98±0.53	NS
MLD, mm	2.44±0.74	1.55±0.70	<0.001
Percent diameter stenosis, %	21±20	49±20	<0.001
Change in MLD			
Acute gain, mm	1.9±0.6 (n=80)	1.9±0.4 (n=25)	NS
Late lumen loss, mm	0.2±0.6 (n=73)	1.1±0.7 (n=23)	<0.0001
Late loss index, %	11±36 (n=73)	55±30 (n=23)	<0.0001
Binary restenosis (>50%)			
Target site	6/73 (8%)	9/23 (39%)	0.0012
Target site plus adjacent segments	17/76 (22%)	12/24 (50%)	0.018

Values are mean±SD unless otherwise indicated.

39% for controls (P=0.0012). Restenosis of segments adjacent to the target site occurred in 11 radiotherapy and 3 control patients. Overall, restenosis of the target site plus adjacent segments occurred in 22% of the radiotherapy group and 50% of the control group (P=0.018).

Results in Stented Arteries

Quantitative coronary angiography showed no significant differences between patients who received stents (n=50) versus those who received balloon angioplasty (n=30) in late lumen loss (0.20±0.50 mm versus 0.25±0.74 mm; P=NS) or in late loss index (9±28% versus 13±46%; P=NS).

Results in 3 Radiotherapy Dose Groups

In patients with follow-up angiography who received 16 Gy (n=23), 20 Gy (n=25), and 24 Gy (n=25), no significant differences existed between groups in late lumen loss (0.12±0.49, 0.31±0.79, and 0.23±0.48 mm, respectively; P=NS), or in late loss index (4±28%, 18±50%, and 10±25%, respectively; P=NS).

Discussion

Endovascular radiotherapy has emerged as a promising method for reducing restenosis.[1–5] Animal investigations using the porcine coronary artery model of restenosis demonstrate a dramatic inhibition of neointima formation after balloon and stent injury after intravascular γ- and β-radiation.[8–16] In a landmark clinical trial, Teirstein and colleagues[2,17] showed a significant reduction in angiographic and clinical measures of restenosis in patients undergoing coronary intervention for restenotic lesions who received γ-radiation (^{192}Ir) compared with a control group.

Using a β-radiation source with more limited penetrability may have inherent safety advantages over γ-radiation sources. β-Radiation, however, has the potential limitation of lesser penetration of the artery wall, particularly in stented arteries.[18] King et al,[4] in a noncontrolled feasibility trial of β-radiation using ^{90}Sr, demonstrated a low late lumen loss and late loss index compared with historical controls in patients with de novo lesions treated with balloon angioplasty followed by radiation with a noncentered source. In clinical practice, however, most coronary interventions include stent implantation, and many coronary interventions are repeated in patients presenting with restenotic lesions.[19]

The present study was undertaken to explore the clinical advantages of an alternative, catheter-based β-radiation system that used a readily available isotope (^{32}P), a centering delivery catheter with perfusion capabilities, and an automated source-delivery unit. In addition, enrollment criteria were expanded to include a broader clinical spectrum of coronary disease, including both de novo (70%) and restenotic lesions (30%); the latter included in-stent restenosis (24%). It should also be noted that the protocol did not dictate the type of interventional procedure. This was left to the discretion of the operator and resulted in a new stent placement in 61% of lesions and balloon angioplasty alone in the other 39%.

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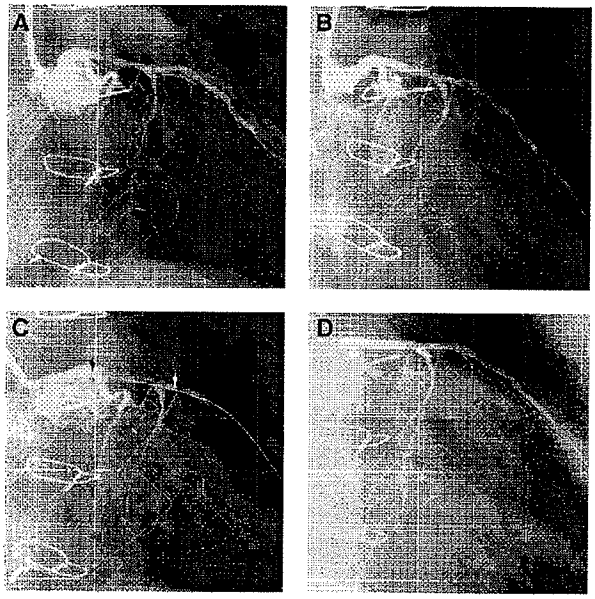

Figure 5. Arteriograms of a patient with in-stent restenosis who had undergone 3 prior interventional procedures, including rotational atherectomy. Despite these efforts, the proximal left anterior descending coronary artery was severely narrowed within the stent (A). After balloon angioplasty, an excellent procedural outcome was achieved (B), after which radiotherapy was applied (C; arrows indicate the radiation zone). At 6-month follow-up angiography (D), the previously recalcitrant restenotic artery has remained widely patent.

The study demonstrates the overall safety and feasibility of β-radiotherapy with this system for the prevention of restenosis. The lack of statistically significant differences in the overall MACE event rates between the 2 groups should not be construed as a negative finding because the study was not powered to show such differences. Individually, the rates of TLR were significantly lower with β-radiotherapy, and the rates of TVR showed a similarly beneficial trend.

The angiographic end points demonstrate a profound inhibition of restenosis within the target site in patients receiving radiotherapy compared with a sham-treated control group. Late lumen loss and the late loss index were reduced 80% by β-radiotherapy with ^{32}P. Angiographic restenosis at the target site was reduced by 79% and the need for revascularization because of target lesion restenosis was reduced by 74%. Importantly, no diminution of effectiveness in arteries in which stents were deployed before radiotherapy treatment seemed to occur. Further, individual instances of previously recalcitrant restenotic lesions, which were prevented from recurring by radiotherapy (Figure 5), underscore the potential utility of intracoronary radiotherapy to inhibit restenosis.

A unique centering catheter was used to center the source in the postangioplasty or stented lumen, facilitating specification of a particular dose at a circumferential layer within the artery wall while, at the same time, allowing perfusion to the distal artery and side branches. In this study, 3 doses (16, 20, and 24 Gy), representing a broad therapeutic spectrum, were used. The effectiveness of radiation to inhibit restenosis at the target site was comparably demonstrated for each of the doses used. This finding offers promise that the spectrum of therapeutic efficacy for radiotherapy is potentially quite wide.

A primary objective of this study was to assess the safety of radiotherapy with the system used. In this regard, 105 of 108 treatments (97%), both active and sham, were successfully administered. Fractionation of the treatment due to a reduction in coronary blood flow by the helical centering balloon was required in only 9% of applications. Only 2 patients had procedure-related clinical events (non–Q-wave MI; 1 patient in each group), which were due to stent-related side branch entrapment. Radiation survey readings in the room at the approximate site of the operator in attendance during active source dwell time were below those encountered during fluoroscopy.

Several potential radiation-related issues were identified in this study. Despite the dramatic inhibition of the restenotic process at the lesion site, which received the full beam of radiation, some patients developed narrowing at or adjacent to the edge of the radiation zone. In most instances in which edge narrowing was observed, a careful review of the procedural angiograms revealed evidence of balloon or stent injury that was incompletely covered by the radiotherapy treatment, which is consistent with the concept of a targeting error or "geographic miss" as the fundamental cause of this phenomenon (Figure 6).[20] As such, incorporating a broad margin of treatment beyond the segment of balloon or stent injury may lessen this phenomenon. In some patients, however, edge narrowing was observed despite radiation treatment that seemed to overlap the injury zone appropriately.

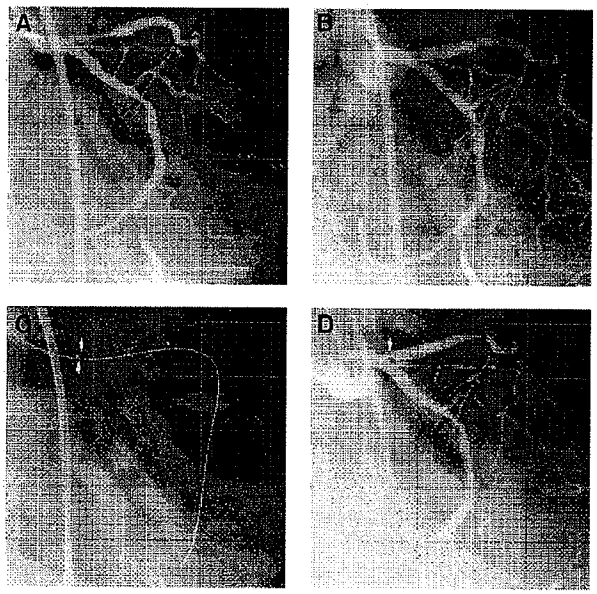

Figure 6. An example of edge narrowing due to geographic miss. This patient, who had a lesion in the proximal left anterior descending artery (A), had a stent placed beginning at the ostium of the artery (B). C, To avoid positioning the radiation catheter in the left main artery, the proximal end of the source (lower arrow) was brought to the edge of the stent (upper arrow), which provided no margin of radiotherapy. At 6-month angiography, edge narrowing was observed precisely at this site (D, arrow). Note that the distal end of the stent that received an adequate margin of radiotherapy shows no evidence of edge narrowing.

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The net effect of edge narrowing was to substantially diminish the overall effectiveness of radiotherapy to inhibit angiographic and clinical measures of restenosis. When angiographic restenosis of the target site alone was analyzed, only 8% of target lesions restenosed. In contrast, when the target site plus adjacent segments was analyzed, the rate of angiographic restenosis in the radiotherapy group increased to 22%. Of note, even with restenosis related to edge narrowing included, the angiographic restenosis rate was still significantly below that observed in the control group (22% versus 50%; $P=0.018$). Similarly, TLR due to restenosis was needed in only 6% of radiotherapy patients. However, revascularization for restenosis at the target lesion or adjacent segments (TVR) was performed in 21% of radiotherapy patients.

An additional observation of this investigation was the occurrence of MI in 7 radiotherapy patients between the time of hospital discharge and 12-month follow-up. No such events occurred in control patients. All 7 MIs seemed to be acute events, which were treated with thrombolytic therapy (6 patients) or direct PTCA (1 patient). Six of the 7 patients had received new stents at the index procedure. These events contributed significantly to the diminution of clinical benefit that might have been anticipated by the impressive reduction in angiographic restenosis. A similar incidence of late thrombosis was recently reported for a group of patients treated in other γ- and β-source trials.[21,22] Although the proximate cause of these late thrombotic events is uncertain, it is reasonable to speculate that radiotherapy delays the formation of "protective" neointima, thus affording an opportunity for exposed stent material or a disrupted lesion to form a nidus for subsequent coronary thrombosis. Reducing the use of new stents in patients who are to receive radiotherapy may be an important strategy to minimize the occurrence of late thrombotic events.

During the time this study was conducted, the standard of care for anti-platelet therapy consisted of aspirin on a continuing basis and ticlopidine for 1 month for stented patients. None of the patients were on ticlopidine at the time a thrombotic event occurred. The possibility that longer-term use of anti-platelet agents would lessen the occurrence of these late thrombotic events is being explored.

Limitations of the Study

This study explored the safety and performance of β-radiation with ^{32}P in a broad spectrum of patients. In view of the limitation in sample size, definitive conclusions, positive or negative, about the efficacy of this radiotherapy to prevent restenosis are limited in scope. Nevertheless, a dramatic reduction of neointimal growth within the target site was demonstrable for this diverse patient group.

In a relatively small population of patients, statistically meaningful comparisons of subgroups are not possible. The subgroup analyses were performed to see if any trends were apparent between subgroups. No such trends were noted among dose subgroups. Additionally, stented patients did not seem to be less responsive than nonstented patients to the effects of radiotherapy.

Conclusions

Radiotherapy with a ^{32}P source wire using a centering catheter method and automated source-delivery unit seems to be safe and highly effective in reducing neointima within the target site in patients undergoing coronary angioplasty. The presence of a metallic stent in the coronary artery did not seem to limit the effectiveness of β-radiotherapy to diminish neointimal growth. There appears to be a wide therapeutic range of safe and effective dosing.

Two radiotherapy-related problems were identified, arterial narrowing adjacent to the edge of the target site and unexpected late coronary thrombo-occlusive events. The use of longer radiotherapy sources that provide a wide margin of treatment beyond the segment of injury may overcome the problem of edge narrowing. More prolonged use of anti-platelet agents and a reduced use of new stents may minimize the occurrence of late thrombotic events. Subsequent large-scale, multicenter trials incorporating these procedural changes will ultimately determine the overall benefit that can be achieved with β-radiotherapy in patients with restenosis.

Acknowledgments

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Exhibit 7

Catheterization and Cardiovascular Diagnosis 45:202–207 (1998)

Basic Investigations

Biocompatibility of Polyurethane-Coated Stents: Tissue and Vascular Aspects

Eldad Rechavia,* MD, Frank Litvack, MD, Michael C. Fishbien, MD, Masato Nakamura, MD, and Neal Eigler, MD

To assess the arterial injury triggered by polyurethane-coated vs. uncoated stents, six polyurethane-coated and six bare nitinol stents were implanted in rabbit carotid arteries. All animals were sacrificed 4 wk after stent placement. Sections were evaluated by histology and morphometric analysis.

At 4 wk, both the coated and uncoated stent struts were entirely endothelialized. The spaces between the struts showed a relatively mild proliferative response, with a few sections demonstrating neovascularization around the struts. Polyurethane coating was associated with an inflammatory tissue response consisting of lymphocytic infiltration and foreign-body reaction, with the appearance of multinucleated giant cells. Lumen, intimal, and medial cross-sectional areas varied little between coated and uncoated stented vessels (2.45 ± 0.19 vs. 2.47 ± 0.47 mm², 1.17 ± 0.52 vs. 0.78 ± 0.30 mm², and 0.66 ± 0.18 vs. 0.58 ± 0.27 mm², respectively).

In the rabbit carotid artery model, polyurethane coating does not affect the degree of neointimal proliferation after endovascular stenting compared with the conventional stenting approach. However, the inflammatory tissue response may indicate a low intrinsic biocompatibility of this stable polymer, so that it may not be an ideal material for coating intravascular devices. *Cathet. Cardiovasc. Diagn. 45:202–207, 1998.*

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Key words: myointimal proliferation; polyurethane; restenosis; stents

INTRODUCTION

Stent implantation is of proven efficacy and safety for the treatment of coronary or saphenous vein graft occlusions [1–5]. However, despite the reduction in restenosis rates, there is apparently no delay in the restenosis process, and myointimal proliferation and late lumen loss are not blunted after endovascular stent implantation [4–9]. The excessive myointimal proliferative response seen with endovascular stenting has prompted clinicians to optimize stent deployment techniques, alter stent design and surface material, and develop new adjunctive strategies, including locally delivered radiation therapy and biocompatible polymers, to deliver drugs locally to the stented arteries.

There is as yet little information on vascular and tissue changes after implantation of stents coated with nonbiodegradable polymers, and it is still unknown whether this approach alters the time course and extent of vascular injury compared with conventional endovascular stenting. Concerns have also been raised regarding the possible induction of neointimal proliferation by the inflammatory reaction to the various biopolymers used for stent coating. The present work was designed to assess the arterial wall response to mechanical injury triggered by

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polyurethane-coated and uncoated stents in a rabbit carotid artery, and to determine whether this synthetic nonbiodegradable polymer is a biocompatible carrier for local stent-mediated drug delivery.

MATERIALS AND METHODS

Stents

Heat-activated removable temporary stents (HARTS™, Advance Coronary Technologies, Inc., Menlo Park, CA) made of the nickel-titanium alloy nitinol were used as coated and uncoated implants [10]. Coated stents were prepared by spraying a commercially available biomedical-grade polyurethane (Tecoflex, Thermetics, Woburn, MA), selected for its properties of membrane formation, flexibility, and biostability, as previously described [11,12]. The average weight of the coating was 5 mg; thickness was 20–30 μm. All stents were mechanically crimped on 3.0-mm-diameter, 20-mm-long balloon catheters (Progressive Angioplasty Systems, Inc., Menlo Park, CA).

Animal Model

Animal experiments conformed to the guidelines of the American Physiological Society and were approved by the Cedars-Sinai Medical Center Institutional Animal Care and Use Committee. Normolipemic adult male New-Zealand White rabbits (3.5–4.0 kg) were anesthetized by intravenous xylazine and ketamine. A 6F sheath was placed in the right femoral artery by cutdown, and heparin (500 units) was given. No antiplatelet agents or additional anticoagulants were administered.

Device-Specific Studies

The rabbits were divided into two groups: group A ($n = 6$) received polyurethane-coated stents, and group B ($n = 6$) received bare nitinol stents. The stents were deployed by two consecutive balloon inflations of 30 sec at 6 atm. The animals were euthanized 28 days after stent placement under general anesthesia, and the carotid artery segments were removed en bloc and pressure-fixed in 10% formalin. Arterial segments containing the stent struts in situ were cut with a diamond wafering blade and embedded in methyl methacrylate [12]. Sections were ground to a thickness of about 30 μm, optically polished, and stained with toluidine blue (paragon stain). Sections were examined by an experienced cardiovascular pathologist (M.C.F.).

Morphometric Analysis

Three to four sections from each vessel were analyzed with a computer-assisted morphometric program (Optimas, Bioscan, Inc.). The mean intimal thickness covering the stent struts and the cross-sectional areas of the lumen, intima, media, and vessel within the external elastic lamina were calculated for each artery. The area occupied by the stent struts was measured and subtracted to yield a net cross-sectional area. Intimal proliferation was also expressed relative to the other measurements, including the ratio of intimal to medial areas and the residual lumen, calculated as the lumen area divided by the sum of the lumen and intimal areas × 100.

Statistical Analysis

The value for each variable within each stented vessel is expressed as mean ± SD. Cross-sectional areas and ratios between coated and uncoated stented vessels were compared by student's t-test. Probability (P) values of <0.05 were considered statistically significant.

RESULTS

Histology

Group A (coated stents). Qualitatively, there was a greater proliferative response to the coated than to the bare stents (Fig. 1). The neointima was composed of morphologic smooth muscle cells, and neovascularization was sometimes prominent around the struts (Fig. 2). The area adjacent to the stent struts showed marked intimal thickening. There was also wide proliferation over the polyurethane conglomerates, which were visible around the struts. This was accompanied by granuloma formation adjacent to the polyurethane collections (Fig. 3) and by local neointimal inflammatory cell infiltration and a foreign-body inflammatory response characterized by multinucleated giant cells (Fig. 4).

Group B (bare stents). At 28 days after implantation, the stent struts were completely covered by neointima in all segments (Fig. 5). Some microscopic organized mural thrombi were present, and an organized intramural hematoma was noted in one section. Sections taken from two arteries showed focal medial necrosis with hemosiderin deposits and segmental breaks of the internal elastic lamina associated with the most deeply implanted struts. Intimal proliferation varied considerably between the regions containing the struts and the intrastrut spaces, with the latter showing relatively milder neointimal thickening.

Quantitative Morphometric Analysis

Table I summarizes the morphometric parameters at 28 days after stent implantation. The intimal layer covering the stent struts and the polyurethane coating had on average a thickness of 110 ± 5 μm and 100 ± 5 μm in coated and uncoated stented arteries, respectively ($P = 0.73$). The lumen, intimal, and medial cross-sectional areas did not differ between the coated and uncoated stented arteries. The intima to media and residual volume ratios were also similar between the two groups (1.71 ± 0.54 vs. 1.59 ± 0.31 and 69 ± 10% vs. 75 ± 8%, respectively).

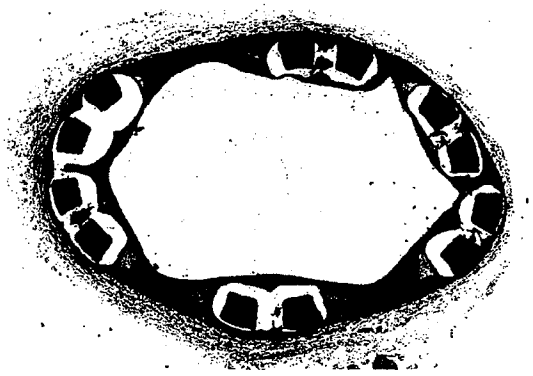

Fig. 1. Section from an artery with an implanted coated stent. The clear space around the struts represents the region occupied by the polyurethane coating, which separates the stent struts and the neointimal proliferation overlying the polyurethane coating.

Fig. 2. Polyurethane-induced wide lymphocytic infiltration and neovascularization between the stent struts.

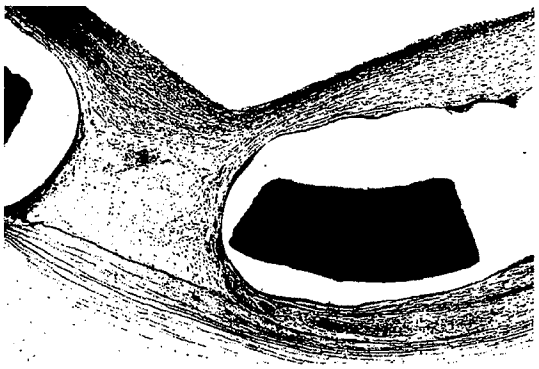

Fig. 3. Granulomatous appearance adjacent to the polyurethane.

Fig. 4. Inflammatory foreign-body response, with multinucleated giant cells surrounding a polyurethane collection.

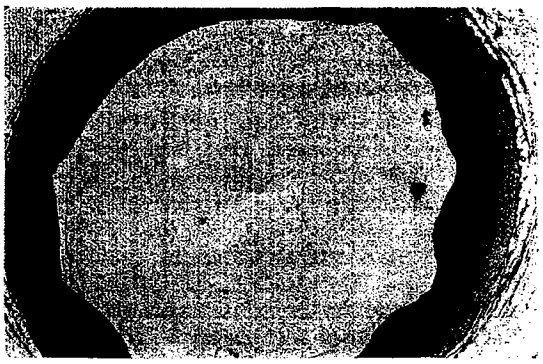

Fig. 5. Representative arterial section, with an implanted bare nitinol stent.

TABLE I. Morphometric Parameters at 28 Days After Stenting: Bare Stents vs. Polyurethane-Coated Stents*

	Stents		
	Coated, no. 6	Uncoated, no. 6	t-test, *P* value
Intimal thickness (μm)	110 ± 4	100 ± 5	0.73
Lumen area (mm^2)	2.47 ± 0.46	2.45 ± 0.19	0.96
Intimal area (mm^2)	1.16 ± 0.51	0.78 ± 0.30	0.18
Medial area (mm^2)	0.66 ± 0.18	0.58 ± 0.27	0.58
Intima/media	1.71 ± 0.54	1.59 ± 0.31	0.66
Residual lumen (%)	69 ± 10	75 ± 8	0.25

*Values are mean ± SD.

DISCUSSION

This study used a rabbit carotid artery model to evaluate the biocompatibility of a commercially available polyurethane as a candidate material for stent-coating. The salient findings are: 1) the polyurethane coating tested in this study does not affect the degree of neointimal proliferation and vascular remodelling at 1 mo after

endovascular stenting; 2) the inflammatory tissue response to coating may have relevance to the selection of this group of biomaterials for coating intravascular devices, including stents; and 3) long-term experiments are needed to verify whether neointimal proliferation is potentiated by the presence of chronic inflammation.

Arterial Wall Response to Polyurethane-Coated and Uncoated Stents

Previous animal model studies have shown that stent implantation creates nonnegligible arterial damage which is associated with more abundant and prolonged neointimal smooth muscle cell proliferation than balloon injury [13–15]. With the growing use of coronary stenting, stent restenosis is becoming increasingly more common. One approach to this problem is to improve the biocompatibility of metallic coronary stents. The Benestent II trial [16] showed that it is possible to find a synthetic polymeric coating which, when combined with an active agent, can be successfully applied to reduce the thrombogenic potential of stents. However, several limitations remain to be overcome. Apart from evidence of the feasibility of using polymer-coated stents for local drug delivery, there are no comprehensive and long-term conclusive data on the biocompatibility of their carriers. For a coated stent to be useful as an intravascular delivery device, compatibility at the blood-tissue interface must be ensured, i.e., the stent should not interfere with wound healing and should not induce either excessive cell proliferation or chronic inflammation. In the present study, both coated and uncoated stented vessels exhibited similar morphometric changes at 28 days after implantation. Although we have no data as yet, it is not inconceivable that polyurethane coating, owing to the tissue inflammatory response it induces, acts as a chronic stimulus, resulting in a prolonged proliferative response even when the stent surface is completely endothelialized. Thus, the overall data on the use of coated stents are incomplete, and limited by the vascular counterreaction these stents elicit and its potential long-term adverse effects. In fact, a recent study in an animal model strongly suggested that the inflammatory reaction observed after implantation of uncoated stents plays a role as important as that of arterial injury in neointimal proliferation [17].

There has also been recent interest in the development of either biostable or biodegradable polymeric compounds that can be implanted within the coronary vasculature to act as a vehicle for local drug delivery for the prevention of subacute thrombosis and long-term restenosis [16,18–22]. Applying a layer of a biocompatible polymer at the interface of the metallic struts within the blood vessel wall, thus excluding direct contact of the metallic stent surface with platelets or clotting factors, may reduce the likelihood of stent thrombosis and the intensity of neointimal proliferation, and at the same time would maintain the mechanical advantages of stenting [23,24]. This approach proved effective in the Benestent II pilot study [16], where stents coated with polyamine plus a dextran sulfate trilayer were implanted in patients with stable angina and de novo lesions. The good results can be attributed to several factors, including the biocompatibility of this polymer, the very thin and uniform application of the coating, and the therapeutic effect of stent-mediated local delivery of heparin. Encouraging clinical results were also observed with silicone-carbide-coated Palmaz-Schatz stents in patients at high risk of stent thrombosis [25]. Rogers and Edelman [23] also provided data indicating that monocyte recruitment, highly regarded as a prominent histological feature of stent-induced neointimal proliferation, was even slightly reduced when stent struts were coated with a biopolymer. In the present study, we assessed polyurethane modulation of the arterial wall response to injury imposed by nitinol stent placement. At 1 mo after deployment, the polyurethane coating was well-preserved (Fig. 1), supporting the intravascular biostability of this polymer. Coated stents had minimal effect on lumen, intimal, and medial cross-sectional areas. These findings are in agreement with previous observations [23,24,26] showing that contact of the stent surface polymer coating with the vessel wall does not affect vascular injury or neointimal thickening. Similarly, De Scheerder et al. [27] found that neither angiographic luminal diameter nor postmortem luminal stenosis differed between groups treated with polyurethane-coated and bare metallic stents. It is noteworthy, however, that a relatively modest tissue reaction toward polyurethane-coated stents as compared with polyphosphazene-coated stents was encountered in their study. This modest reaction is in apparent contradiction to the intense inflammatory response which we observed. Although this type of post hoc comparison is invalid to a certain extent, the heterogeneity in tissue response among the various studies stems largely from the fact that polyurethanes are a diverse group of biomaterials with distinct biological properties and interactions with the surrounding vascular tissue. Therefore, the results of the present study may be applicable only to the specific polymer studied. Nonetheless, one may still question whether the majority of polyurethane compounds are ideal inert biocompatible materials despite their apparently favorable vascular effects [11,23]. The unfavorable tissue response observed in our study, which does not seem to be different from histological features noted in other studies [19,28], raises concerns regarding the use of this class of biopolymers for coating intravascular devices, including coronary stents, although presently there is no compelling evidence indicating that the inflammatory response actively affects late neointimal proliferation and luminal loss.

Study Limitations

In the present model, there were no preexisting atheromatous lesions, and the animals were fed a normal diet. This model may have potential limitations even though hyperlipidemia and atheromatous lesions are not a prerequisite for the production of neointimal proliferation after vessel injury. Also, no angiography or intravascular ultrasound studies were performed to guide stent size. We selected the 3.0-mm stent as adequate for optimal implantation, based on our previous use of a 3.0-mm balloon to create vessel injury.

CONCLUSIONS

This report describes the morphologic and morphometric changes that occur in rabbit carotid arteries after placement of polyurethane-coated and uncoated nitinol stents. After 28 days, implantation of the coated stents was associated with an inflammatory tissue response which may be indicative of a low intrinsic biocompatibility of this polymer. This finding suggests that the polymer studied here is far from an ideal coating material for intravascular devices, including coronary stents. Are these data sufficiently compelling to warrant abandonment of polyurethane stent coating? We emphasize that only one polyurethane compound was studied here, and it is premature to discount the potentially effective role of stent coating with idealized biomaterials, with or without adjunctive therapy. Longer-term biocompatibility studies are warranted, not only to assess the biocompatibility of various polymers, but also to detect whether the presence of a chronic inflammatory reaction after implantation of coated stents promotes neointimal proliferation and, if so, to determine the magnitude of this response.

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Angiographic Findings of the Multicenter Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL): Sirolimus-Eluting Stents Inhibit Restenosis Irrespective of the Vessel Size

E. Regar, P.W. Serruys, C. Bode, C. Holubarsch, J.L. Guermonprez, W. Wijns, A. Bartorelli, C. Constantini, M. Degertekin, K. Tanabe, C. Disco, E. Wuelfert, M.C. Morice and on Behalf of the RAVEL Study Group

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Angiographic Findings of the Multicenter Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL)

Sirolimus-Eluting Stents Inhibit Restenosis Irrespective of the Vessel Size

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Background—Restenosis remains the major limitation of coronary catheter-based intervention. In small vessels, the amount of neointimal tissue is disproportionately greater than the vessel caliber, resulting in higher restenosis rates. In the Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL) trial, ≈40% of the vessels were small (<2.5 mm). The present study evaluates the relationship between angiographic outcome and vessel diameter for sirolimus-eluting stents.

Methods and Results—Patients were randomized to receive either an 18-mm bare metal Bx VELOCITY (BS group, n=118), or a sirolimus-eluting Bx VELOCITY stent (SES group, n=120). Subgroups were stratified into terciles according to their reference diameter (RD; stratum I, RD <2.36 mm; stratum II, RD 2.36 mm to 2.84 mm; stratum III, RD >2.84 mm). At 6-month follow-up, the restenosis rate in the SES group was 0% in all strata (versus 35%, 26%, and 20%, respectively, in the BS group). In-stent late loss was 0.01±0.25 versus 0.80±0.43 mm in stratum I, 0.01±0.38 versus 0.88±0.57 mm in stratum II, and −0.06±0.35 versus 0.74±0.57 mm in stratum III (SES versus BS). In SES, the minimal lumen diameter (MLD) remained unchanged (Δ −0.72 to 0.72 mm) in 97% of the lesions and increased (=late gain, ΔMLD <−0.72 mm) in 3% of the lesions. Multivariate predictors for late loss were treatment allocation ($P<0.001$) and postprocedural MLD ($P=0.008$).

Conclusions—Sirolimus-eluting stents prevent neointimal proliferation and late lumen loss irrespective of the vessel diameter. The classic inverse relationship between vessel diameter and restenosis rate was seen in the bare stent group but not in the sirolimus-eluting stent group. **(*Circulation.* 2002;106:1949-1956.)**

Key Words: stents ■ drugs ■ angioplasty ■ restenosis

Restenosis remains the major limitation of coronary catheter-based intervention.[1] In stented vessels, the major contributor to restenosis is neointimal proliferation, which is a ubiquitous, local, vascular reaction to catheter-induced vessel injury.[2] Vessel diameter is an established predictor of angiographic outcome after catheter-based intervention, with a higher restenosis rate in smaller vessels.[3] This is because of the disproportionately greater amount of neointimal tissue relative to the vessel caliber.[4] Although coronary stents provide major benefits versus simple balloon angioplasty by inhibiting acute vessel closure, early vessel recoil, and late vessel constriction, they stimulate neointimal proliferation. Therefore, restenosis rates in small vessels may be similarly high with these 2 treatment modalities.[5,6] Inhibition of neointimal proliferation by local pharmacological interventions is a promising concept. Sirolimus (rapamycin) is an immunosuppressive drug approved for the prevention of renal transplant rejection. It also has potent antiproliferative and antimigratory effects on vascular smooth muscle cells.[7] Recent clinical experience with sirolimus-eluting coronary stents has shown excellent results, with 0% restenosis at 4-month,[8] 6-month,[9] and 12-month follow-up.[10] At the time of these pilot studies, sirolimus-eluting stents were only available in a 3.0-mm or 3.5-mm diameter, limiting treatment to relatively large vessels. In the Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL) trial, a smaller sirolimus-eluting stent with a diameter of 2.5 mm was available, and it allowed smaller

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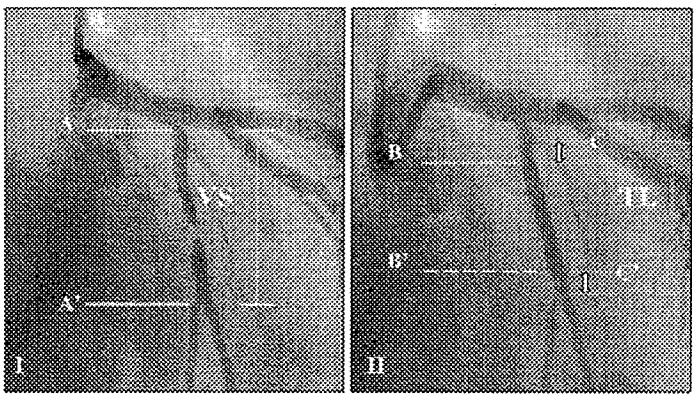

Figure 1. I, Vessel segment (VS) was defined as the segment bounded by side branches proximal (A) and distal (A') to the stent segment. II, Target lesion (TL) encompassed the stent segment and edge segments. The length of the vessel covered by stent struts defined the stent segment (from B to B'). The edge segments encompassed the vessel 5 mm proximal (C) and distal (C') to the stent.

vessels to be stented. This small sirolimus-eluting stent was used in 18% of patients.[11] The present study investigated the relationship between angiographic outcome and vessel diameter for sirolimus-eluting stents compared with bare metal stents.

Methods

Patients and Stent Implantation

The patient population and stent implantation technique have been described in detail elsewhere.[11] The 238 patients enrolled in the RAVEL trial had a single de novo lesion of a native coronary artery.

Patients were randomized (double-blind) for implantation of either an 18-mm uncoated bare metal Bx VELOCITY stent (BS), or a sirolimus-eluting Bx VELOCITY balloon-expandable stent (Cordis Corp, Johnson & Johnson) (SES). All drug-eluting Bx VELOCITY stents contained 140 μg sirolimus/cm^2 ($\pm$10%). Total sirolimus content was 153 μg ($\pm$10%) on the 6-cell stent (2.5 and 3.0 mm in diameter) and 180 μg ($\pm$10%) on the 7-cell stent (3.5 mm in diameter). This difference in content was due to the differences in the surface area of the two stents. Stent implantation was performed in the conventional manner after predilation. Postdilatation was performed as necessary to achieve a residual stenosis below 20% with TIMI grade III flow. Patients received aspirin (at least 100 mg) indefinitely with either clopidogrel (75 mg daily) or ticlopidine (250 mg, twice daily) for 8 weeks.

Quantitative Coronary Angiographic Analysis

Coronary angiograms were obtained in multiple views after intracoronary injection of nitrates. Quantitative analyses by edge-detection techniques were performed by an independent core laboratory (Cardialysis BV) blinded to treatment allocation. Reference diameter (RD), minimal luminal diameter (MLD), and degree of stenosis (as percentage of diameter) were measured before dilatation, at the end of the procedure, and at a 6-month follow-up. Restenosis was defined as >50% diameter stenosis at follow-up. Late loss was defined as MLD after the procedure minus MLD at follow-up.

The target lesion was defined as the stent segment plus 5 mm proximal and 5 mm distal to the edge of the stent. The vessel segment was defined as the segment bounded by side branches proximal and distal to the stent segment (Figure 1).

The accuracy of the method has been reported in detail.[12] Given the accuracy of quantitative coronary angiography for MLD measurements, we used 2 standard deviations[12] as the cut-off point for the classification of late loss indicating whether MLD was unchanged (no loss, ΔMLD -0.72 to 0.72 mm), reduced (late loss, ΔMLD >0.72 mm), or larger (late gain, ΔMLD <-0.72 mm, "negative late loss") at follow-up.[13]

Subgroup Definition

Both groups were stratified according to their vessel diameter. Vessel diameter was defined as the baseline RD in the vessel segment analysis before intervention. The terciles for the RD were calculated and used as cut-off points for subgroup definition.

Sample Size Estimation and Statistical Analysis Based on Late Loss

A sample size of 95 in each group had 87% power to detect a difference in means of 0.25 mm (the difference between a bare stent late loss mean, μ_B, of 0.80 mm and a sirolimus stent late loss mean, μ_S, of 0.55 mm), assuming that the common standard deviation is 0.55 using a 2-group t test with a 0.05 1-sided significance level. The sample size was increased to 110 in each group to account for noncompliance to 6-month angiographic follow-up.

Data are presented as mean$\pm$SD or proportions. For comparison of continuous data, a 2-tailed Student's t test was performed. A value of $P<0.05$ was considered significant. To identify the factors that might be related to late lumen loss, linear regression analyses were performed. Predictors were chosen by stepwise linear regression using an entry criterion of 0.20 and a stay criterion of 0.05.

Results

The 238 patients were randomly assigned (SES, n=120; BS, n=118). There were no significant differences with regard to procedural success (96.6% versus 93.1%), stents per patient (1.0$\pm$0.3 versus 1.1$\pm$0.3), and nominal stent diameter (3.06$\pm$0.34 mm versus 3.10$\pm$29 mm; SES versus BS, respectively).

Before the procedure, RD (2.60$\pm$0.54 mm versus 2.64$\pm$0.52 mm) and MLD (0.94$\pm$0.31 mm versus 0.95$\pm$0.35 mm) were similar in both groups. After the procedure, there were also no meaningful differences (postprocedural RD, 2.62$\pm$0.44 mm versus 2.68$\pm$0.45 mm; postprocedural MLD, 2.43$\pm$0.41 mm versus 2.41$\pm$0.40 mm; SES versus BS, respectively). At follow-up, the SES group showed a larger MLD (2.42$\pm$0.49 mm versus 1.64$\pm$0.59 mm, $P<0.001$) and lower late lumen loss (-0.01 ± 0.33 mm versus 0.80$\pm$0.53 mm, $P<0.001$). Binary restenosis was 0.0% in the SES group and 26.6% in the BS group ($P<0.001$).

Figure 2 illustrates the relation between postprocedural MLD and MLD at follow-up. In the SES group, the MLD (Figure 2A) remained basically unchanged; late loss was seen in 1 lesion and late gain was seen in 4 lesions (3%). In contrast, lumen reduction over time was seen in approximately half of the BS patients (n=55, 47%), and no late gain

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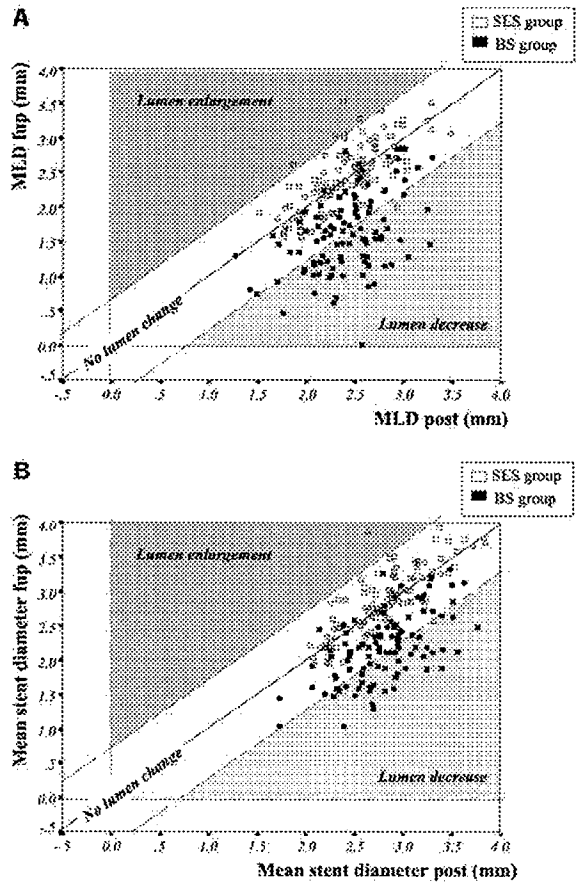

Figure 2. Relationship between measurements after implantation and at 6-month follow-up for the SES group and the BS group: MLD (A), mean diameter over the entire length of the stent (B). Dashed lines indicate the range of ±0.72 mm change in diameter.

was seen. A similar pattern was found for the mean diameter over the entire length of the stent (Figure 2B).

Stratification

Subgroups were stratified according to their RD (Figure 3). There were no significant differences in baseline patient and lesion characteristics in the SES and BS subgroups. There were also no significant differences in procedural parameters (Table 1).

Analysis of the strata revealed a higher proportion of diabetic patients in small and intermediate vessels. The stent implantation procedure showed a decreasing balloon to artery ratio (stratum I versus stratum III: $P<0.001$ in both, BS and SES group) and increasing inflation pressure from stratum I to stratum III (stratum I versus stratum III: $P<0.01$ SES group; $P=0.22$ BS group).

Table 2 summarizes the key angiographic data. Vessel segment analysis showed similar preprocedural and postprocedural MLD in both treatment groups throughout corresponding strata.

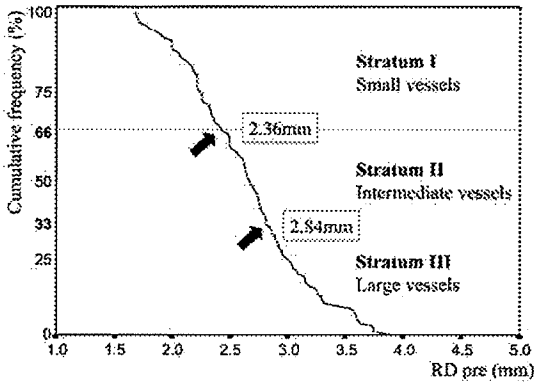

Figure 3. Subgroup stratification: cumulative frequency distribution curve of the preinterventional reference diameter. Arrows indicate cut-off values at the 33rd and the 66th percentile.

Restenosis, Late Lumen Loss, and Vessel Size

At follow-up, the MLD was consistently larger in the SES groups. In all strata, the restenosis rate was 0% in the SES groups, with extremely low and consistently uniform late loss. In the BS strata, the classic inverse relationship between restenosis rate and vessel diameter was seen. Restenosis rate virtually doubled with decreasing vessel size from 20% in large vessels (stratum III) to 35% in small vessels (stratum I). The amount of late loss, however, was similar in the 3 groups (0.80 mm in stratum I, 0.88 mm in stratum II, and 0.74 mm in stratum III). Therefore, the observed increase in restenosis rate in smaller vessels in this series is driven largely by the relative amount of obstruction as a function of vessel diameter rather than being due to an absolute increase in neointimal hyperplasia in smaller vessels.

Subsegment Analysis

Vessel Segment Analysis

Vessel segment analysis revealed minimal late gain in both the MLD and RD over time in SES subgroups but not in BS groups (Table 2).

Target Lesion Analysis (Including Stent Segment and the Proximal and Distal Edges)

The SES subgroups showed minimal late loss at the stent segment (0.01±0.25 mm, 0.01±0.38 mm, and −0.06±0.35 mm in strata I, II, and III, respectively) and proximal edges (0.04±0.34 mm, 0.08±0.42 mm, and 0.03±0.43 mm in strata I, II, and III, respectively), whereas the distal SES edges had minimal late gain (−0.05±0.29 mm, −0.14±0.31 mm, and −0.09±0.31 mm in strata I, II, and III, respectively). In contrast, the BS subgroups showed pronounced late loss in the stent segment and moderate late loss at the proximal and distal edges.

Multivariate Analysis

Univariate predictors for late loss included treatment allocation and postprocedural MLD (Table 3). Multivariate predictors for late loss were treatment allocation ($P<0.001$) and the MLD after the procedure ($P=0.008$) (Table 4).

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TABLE 1. Baseline Characteristics for Sirolimus-Eluting and Bare Stents, Stratified by Vessel Size

Stratum/Parameter	SES	BS	Difference (95% CI)	P
I				
n	42	37	...	...
Age, y	62±12	62±10	−0.4 (−5.0, 4.3)	...
Male sex	73.8	75.7	−1.9 (−21.0, 17.3)	...
Diabetes mellitus	19.0	27.0	−8.0 (−26.6, 10.6)	...
Unstable angina	40.4	48.6	−8.1 (−30.0, 13.7)	...
Lesion length, mm	9.5±3.2	8.8±2.8	0.70 (−0.64, 2.04)	...
Discrete (<10 mm)	64.3	64.9	−0.6 (−21.7, 20.6)	...
Tubular (10–20 mm)	35.7	35.1	0.6 (−20.6, 21.7)	...
Lesion type (AHA/ACC)				
A	9.5	2.7	6.8 (−3.5, 17.1)	...
B1	28.6	32.4	−3.9 (24.2, 16.5)	...
B2	61.9	64.9	−3.0 (−24.2, 18.3)	...
C	0	0	0	...
Mean stent diameter, mm	2.8±0.2	2.9±0.2	−0.10 (−0.22, 0.01)	0.08
3.5	2.3	5.4	−3.0 (−11.6, 5.4)	0.59
3.0	58.1	73.0	−14.8 (−35.3, 5.7)	0.24
2.5	39.5	21.6	17.9 (−1.8, 37.6)	0.10
Balloon-artery ratio	1.3±0.1	1.3±0.2	0 (−0.09, 0.09)	0.96
Maximal inflation pressure, atm	14.2±3.5	14.2±3.4	−0.03 (−1.5, 1.5)	0.97
Postprocedural dissection				1.00
None	76.2	75.7	0.5 (−18.4, 19.4)	...
Type A	7.1	2.7	4.4 (−4.9, 13.8)	...
Type B	9.5	18.9	−9.4 (−24.8, 6.0)	...
Type C	7.1	2.7	4.4 (−4.9, 13.8)	...
Other	0	0	0	...
II				
n	40	38	...	...
Age, y	61±10	59±11	1.3 (−3.5, 6.2)	...
Male sex	72.5	81.6	−9.1 (−27.6, 9.5)	...
Diabetes mellitus	22.5	21.1	1.4 (−16.9, 19.8)	...
Unstable angina	51.2	54.0	−2.7 (−25.2, 19.6)	...
Lesion length, mm	9.0±2.9	8.4±2.2	0.54 (−0.62, 1.70)	...
Discrete (<10 mm)	89.5	83.8	5.7 (−9.7, 21.1)	...
Tubular (10–20 mm)	10.5	18.9	−8.7 (−24.5, 7.1)	
Lesion type (AHA/ACC)				
A	5.1	5.4	−0.3 (−10.3, 9.8)	...
B1	53.8	35.1	18.7 (−3.2, 40.7)	...
B2	41.0	59.5	−18.4 (−40.5, 3.7)	...
C	0	0	0	...
Mean stent diameter, mm	3.0±0.3	3.1±0.2	−0.03 (−0.16, 0.09)	0.60
3.5	26.1	26.3	−0.1 (−19.4, 19.1)	1.00
3.0	61.9	68.4	−6.5 (−27.3, 14.3)	0.64
2.5	11.9	5.2	−6.6 (−5.4, 18.7)	0.44
Balloon-artery ratio	1.1±0.1	1.2±0.2	−0.1 (−0.1, −0.03)	0.008
Maximal inflation pressure, atm	14.7±3.1	15.5±2.6	−0.7 (−2.0, 0.5)	0.26
Postprocedural dissection				0.62
None	71.8	64.9	6.9 (−14.0, 27.8)	...
Type A	10.3	21.6	−11.4 (−27.7, 5.0)	...
Type B	7.7	8.1	−0.4 (−12.6, 11.7)	...
Type C	5.1	2.7	2.4 (−6.2, 11.1)	...

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TABLE 1. (Continued)

Stratum/Parameter	SES	BS	Difference (95% CI)	P
Other	5.1	0	5.1 (−1.8, 12.1)	...
III				
n	38	42	...	...
Age, y	62±9	57±9	5.3 (1.2, 9.4)	...
Male sex	63.2	88.1	−24.9 (43.1, −6.7)	...
Diabetes mellitus	5.3	16.7	−11.4 (−24.7, 1.9)	...
Unstable angina	54.0	52.3	1.6 (−20.3, 23.7)	...
Lesion length, mm	10.1±3.8	11.4±3.4	−1.27 (−2.91, 0.38)	...
Discrete (<10 mm)	85.7	74.4	11.4 (−6.6, 29.3)...	
Tubular (10–20 mm)	14.3	25.6	−11.4 (−29.3, 6.6)	...
Lesion type (AHA/ACC)				
A	7.9	4.8	3.1 (−7.6, 13.9)	...
B1	34.2	35.7	−1.5 (−22.4, 19.4)	...
B2	57.9	59.5	−1.6 (−23.2, 20.0)	...
C	0	0	0	...
Mean stent diameter, mm	3.3±0.2	3.2±0.2	0.07 (−0.04, 0.18)	0.22
3.5	64.9	51.2	13.7 (−7.7, 35.1)	0.26
3.0	35.1	48.8	−13.7 (−35.1, 7.7)	0.26
2.5	0	0	0	...
Balloon-artery ratio	1.0±0.1	1.0±0.1	0.03 (−0.05, 0.10)	0.51
Maximal inflation pressure, atm	16.2±3.6	15.1±3.2	1.0 (−0.4, 2.5)	0.18
Postprocedural dissection				0.76
None	86.8	83.3	3.5 (−12.1, 19.1)	...
Type A	0	7.1	−7.1 (−14.9, 0.6)	...
Type B	7.9	9.5	−1.6 (−14.0,, 10.7)	...
Type C	5.3	0	5.3 (−1.8, 12.4)	...
Other	0	0	0	...

AHA/ACC indicates American Heart Association/American College of Cardiology classification.

Discussion

We investigated the relationship between vessel diameter and angiographic outcome 6 months after sirolimus-eluting stent implantation in patients in the RAVEL trial. The main findings of the study are that sirolimus-eluting stents prevent restenosis irrespective of vessel diameter and do not show the classic inverse relationship of vessel diameter to restenosis rate.

Quantitative coronary angiography convincingly demonstrates the absence of neointimal proliferation and restenosis in all patients treated with the sirolimus-eluting stent within the first 6 months, unlike those treated with bare metal stents. This truly remarkable finding creates a totally new paradigm in interventional cardiology and puts paid to the well-established existing paradigm, the classic inverse relationship between vessel diameter and restenosis rate.[3]

Prevention of Neointima Growth

Neointimal growth is a normal reaction to vascular injury. Smooth muscle cells are considered to be the main components of coronary artery neointima after stent implantation, and the severity of the reaction may be modulated by the extent of stent-induced vessel injury[14] and the inflammatory reaction around the stent struts.[15]

Vessel injury is influenced by stent surface material, geometric configuration, implantation technique, and vessel size.[16] Neointimal hyperplasia and persistent tissue proliferation are related to the degree of vessel injury (balloon/artery ratio×inflation pressure).[17]

In our patients, 2 stent configurations (6-cell and 7-cell designs) were used. Stent implantation technique varied with vessel size. In small vessels, a relatively higher balloon to artery ratio of 1.3 was achieved, whereas the balloon to artery ratio was lower (1.0) in large vessels. Conversely, the inflation pressure was lower in small vessels than in larger vessels (14 atm versus 16 atm).

In the present study, the effectiveness of the sirolimus-eluting stent was extremely strong and was affected neither by established risk factors for restenosis nor by stent configuration, balloon to artery ratio, or balloon pressure. Other than treatment allocation, the only independent predictor for late loss was the postprocedural MLD.

The very low late loss, which is consistently reported in all studies with sirolimus-eluting stents,[8–10] raised concerns about late lumen enlargement. In the present study, there was evidence of late lumen gain (negative late lumen loss) in 3% of SES patients.

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TABLE 2. Quantitative Coronary Angiography Analysis of Sirolimus-Eluting Stents and Bare Stents, Stratified by Vessel Size

					Target Lesion			
	Vessel Segment		Stent Segment		Proximal Edge		Distal Edge	
Stratum/Parameter	SES	BS	SES	BS	SES	BS	SES	BS
I								
RD, mm								
Before	2.09±0.21	2.07±0.21	...	...	...	...	...	...
After	2.30±0.30	2.26±0.33	2.38±0.26	2.40±0.31	...	...	...	...
Follow-up	2.34±0.42	2.11±0.33	2.45±0.38	2.12±0.32	...	...	...	...
MLD, mm								
Before	0.82±0.19	0..77±0.18	0.82±0.19	0.77±0.18	1.84±0.38	1.71±0.40	1.53±0.31	1.56±0.36
After	1.66±0.30	1.57±0.30	2.05±0.25	2.06±0.29	2.01±0.37	1.95±0.33	1.82±0.31	1.71±0.33
Follow-up	1.69±0.38	1.20±0.37	2.04±0.32	1.26±0.41	1.96±0.42	1.73±0.43	1.85±0.35	1.69±0.41
RR, %	0	35	...	...	...	...	...	...
LL, mm	−0.04±0.29	0.37±0.37	0.01±0.25	0.80±0.43	0.04±0.34	0.20±0.46	−0.05±0.29	0.03±0.45
II								
RD, mm								
Before	2.58±0.14	2.60±0.14	...	...	...	...	...	...
After	2.60±0.27	2.71±0.34	2.74±0.21	2.81±0.25	...	...	...	...
Follow-up	2.77±0.47	2.62±0.31	2.84±0.42	2.58±0.24	...	...	...	...
MLD, mm								
Before	0.97±0.26	0.94±0.21	0.97±0.26	0.94±0.21	2.29±0.44	2.19±0.50	2.00±0.38	2.08±0.40
After	1.99±0.26	2.06±0.32	2.45±0.27	2.41±0.25	2.45±0.31	2.48±0.33	2.09±0.31	2.22±0.36
Follow-up	2.06±0.43	1.58±0.50	2.44±0.39	1.59±0.53	2.38±0.47	2.13±0.45	2.23±0.45	2.13±0.32
RR, %	0	26	...	...	...	...	...	...
LL, mm	−0.07±0.35	0.56±0.51	0.01±0.38	0.88±0.57	0.08±0.42	0.40±0.39	−0.14±0.31	0.14±0.41
III								
RD, mm								
Before	3.25±0.38	3.22±0.30	...	...	...	...	...	...
After	2.99±0.43	3.01±0.33	3.18±0.34	3.19±0.29	...	...	...	...
Follow-up	3.09±0.45	2.91±0.50	3.29±0.32	2.97±0.49	...	...	...	...
MLD, mm								
Before	1.04±0.41	1.13±0.47	1.04±0.41	1.13±0.47	2.75±0.59	2.75±0.59	2.47±0.46	2.55±0.50
After	2.31±0.36	2.35±0.27	2.81±0.28	2.73±0.31	2.98±0.38	2.89±0.45	2.51±0.50	2.65±0.32
Follow	2.35±0.33	1.89±0.46	2.86±0.37	2.01±0.56	2.96±0.32	2.64±0.62	2.60±0.45	2.47±0.43
RR, %	0	20	...	...	...	...	...	...
LL, mm	−0.06±0.25	0.47±0.50	−0.06±0.35	0.74±0.57	0.03±0.43	0.27±0.56	−0.09±0.31	0.18±0.43

RR values are given as percentages; all other values are mean±SD in millimeters.
RR indicates restenosis rate; and LL, late lumen loss.

Furthermore, minimal but consistently negative late loss was seen at the distal edges of the stent. This phenomenon might be related to the downstream elution of the drug.

Although the finding of late lumen gain in a very small percentage of patients is interesting, it is worth noting that there have been no clinical events attributable to this phenomenon in the patients treated with the sirolimus-eluting stent at 1-year follow-up, or in the patients of Sousa et al[10] for up to 2 years. Mechanistic angiographic analysis of the Sao Paulo series[10] showed stable lumen dimensions with minimal late lumen loss between 4- and 12-month follow-up (in-stent MLD 2.90±05 mm at 4 months and 2.87±0.4 mm at 12 month; slow-release group) that matches well with the stable clinical result.

The Importance of Late Loss as a Predictor of Restenosis

The classic inverse relationship between vessel diameter and restenosis rate was not seen in the sirolimus-eluting stent group. This offers new therapeutic options for small vessels, in which conventional stenting is of questionable value.[5] This is especially true for diabetic patients, who often have small arteries because of diffuse coronary artery disease.[18] In addition, they frequently have an exaggerated neointimal

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TABLE 3. Univariate Predictors of Late Loss for All Patients Treated

Univariate Predictor of Late Loss	Parameter	Standard Error	R2	P
Treatment	0.814371	0.059535	0.4653	<0.001*
MLD after procedure, mm	0.223776	0.100029	0.0227	0.026*
Age, y	−0.00724	0.003924	0.0156	0.066
Total length of stents, mm	0.021843	0.012981	0.0130	0.094
Eccentric IB lesion before procedure	−0.13079	0.087642	0.0106	0.137
Smoking, previous or current	−0.12488	0.088079	0.0093	0.158
Diabetes mellitus	0.144408	0.103526	0.0090	0.165
Number of stents	0.222425	0.168080	0.0081	0.187
Thrombus lesion before procedure	−0.28244	0.230559	0.0072	0.222
MLD before procedure, mm	0.148352	0.121476	0.0069	0.223
Diameter stenosis after procedure, %	−0.03379	0.003864	0.0045	0.328
Lesion type B2	0.075694	0.082215	0.0039	0.358
Diameter stenosis after procedure, %	−0.00591	0.006459	0.0039	0.361
QCA lesion length before procedure, mm	0.011469	0.012559	0.0040	0.362
Unstable angina at screening	0.072019	0.082139	0.0036	0.382
Male sex	0.080158	0.096519	0.0032	0.407
Hypertension	0.064092	0.081323	0.0029	0.432
Eccentric 1A lesion before procedure	0.064127	0.084667	0.0028	0.450
Eccentric IIa lesion before procedure	0.102716	0.138269	0.0026	0.458
Previous PTCA	−0.07700	0.108119	0.0024	0.477
Previous CABG	−0.20522	0.348366	0.0016	0.556
Hypercholesterolemia	−0.04599	0.081463	0.0015	0.573
Eccentric IIB lesion before procedure	0.090999	0.186324	0.0011	0.626
LAD treated	−0.03735	0.081421	0.0010	0.647
Readily accessible lesion before procedure	0.052347	0.132952	0.0007	0.694
Previous myocardial infarction	0.020693	0.084594	0.0003	0.807
Calcification (moderate/heavy) before procedure	−0.01526	0.096575	0.0001	0.875
Reference diameter before procedure, mm	0.003010	0.076780	0.0000	0.969

Predictors were chosen by stepwise linear regression using an entry criterion of 0.20 and a stay criterion of 0.05.

QCA indicates quantitative coronary angiography; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; and LAD, left anterior descending artery.

*Significant.

proliferative response that manifests as significantly greater late loss at the treatment site and a resultant 2-fold increase in in-stent restenosis in small vessels (44% versus 23%, $P=0.002$) as compared with nondiabetic patients with similar-sized vessels.[19] In our study, diabetes mellitus did not attenuate the effectiveness of the sirolimus-eluting stent. These findings contrast markedly with what was seen in the bare stent group. Restenosis rates almost doubled from the tertile with the largest diameter vessels to the one with the smallest vessels (20% to 35%), whereas late loss increased only modestly (0.74 mm to 0.80 mm). This dramatic increase in restenosis rate is explicable on the basis of hydraulics. A late loss of 0.80 mm in a 3.0-mm diameter vessel versus a 2.0-mm diameter vessel results in a 46% versus a 64% obstruction. Late loss is the most sensitive and operator-independent assessment of the effect of drug-eluting stents and can be used to predict what the restenosis rate will be in vessels of different diameters. Simply reporting angiographic restenosis rates, which can be influenced by case selection and operator techniques, is no longer sufficient in the era of drug-eluting stents.

TABLE 4. Multivariate Predictors of Late Loss

Multivariate Predictor of Late Loss	Parameter	Standard Error	R2	P
Treatment	0.810123	0.058706	0.4653	0.0001*
MLD after procedure, mm	0.196763	0.072959	0.4829	0.0076*

Predictors were chosen by stepwise linear regression using an entry criterion of 0.20 and a stay criterion of 0.05.

*Significant *P* value.

Conclusion

Sirolimus-eluting stents prevent neointimal proliferation and late lumen loss irrespective of the vessel size. The classic inverse relationship between vessel diameter and restenosis rate was seen in the bare stent group but not in the sirolimus-

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eluting stent group. This finding with the sirolimus-eluting stent has the potential to considerably expand the use of these stents in smaller vessels and to eliminate the present difference in reintervention rates between patients treated with coronary artery bypass surgery and stenting.[20]

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